UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

FROM: Warren Lux
EPA Human Subjects Research Review Official

OFFICE OF THE
SCIENCE ADVISOR

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Approval of Research Involving Human Subjects

DATE: March 6, 2012

I have reviewed the study cited below according to the requirements of EPA Order 1000.17 Change A1 **(Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research)** and have determined that it qualifies as intentional exposure research involving human subjects that complies with EPA Regulation 40 CFR 26 **(Protection of Human Subjects)**. The finding of compliance includes the determination that the research is non-exempt under 40 CFR 26.101(b), that it has been approved by the IRB of record, and that the institution engaged in the research has a valid Federalwide Assurance on file with the HHS Office for Human Research Protections. Accordingly, approval is granted for recruitment and enrollment of human research subjects into the study.

Study Title:	*Cardiopulmonary Effects of Exposure of Healthy Older GSTM1 Null and Sufficient Individuals to Concentrated Ambient Air Particles (CAPTAIN)*
Engaged Institution:	U.S. Environmental Protection Agency, National Health & Environmental Effects Research Laboratory
FWA #:	FWA00012755
UNC IRB Protocol #:	11-1807
Principal Investigator:	James Samet
HSRRO Study #:	C12-020CS

CC: Deepika Polineni, Director, NHEERL Human Research Protocol Office

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF THE
SCIENCE ADVISOR

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Approval of Research Involving Human Subjects

DATE: October 25, 2011

I have reviewed the study cited below according to the requirements of EPA Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as research involving human subjects that complies with EPA Regulation 40 CFR 26 (**Protection of Human Subjects**). The finding of compliance includes the determination that the research is non-exempt under 40 CFR 26.101(b), that it has been approved by the IRBs of record, and that the institutions engaged in the research have valid Federalwide Assurances on file with the HHS Office for Human Research Protections. Accordingly, approval is granted for recruitment and enrollment of human research subjects into the study.

Study Title:	*The Role of TGF-Beta in Asthmatic Epithelial Cell Susceptibility to RSV Infection*
Engaged Institutions:	National Institutes of Health, NIEHS U.S. Environmental Protection Agency, NHEERL
FWA#s:	FWA00005897 (NIH) FWA00012755 (U.S. EPA)
Principal Investigator:	Stavros Garantziotis
HSRRO SAA#:	C10-019F
HSRRO Study#:	J11-071CS

CC: Deepika Polineni

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF THE
SCIENCE ADVISOR

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Contingent Approval of Research Involving Human Subjects

DATE: January 26, 2010

I have reviewed the project cited below according to the requirements of EPA Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as intentional exposure research involving human subjects that will comply with EPA Regulation 40 CFR 26 (**Protection of Human Subjects**) if the exclusion criteria for the project are extended to cover pregnant and nursing women, as well as children. Approval is therefore granted for enrollment of human research subjects into the study contingent upon modifying the exclusion criteria accordingly.

Project Title:	*Blood Endpoints in Non-Exercising Volunteers*
Principal Investigator:	Andrew Ghio
Engaged Institution:	U.S. Environmental Protection Agency (National Health and Environmental Effects Research Laboratory)
FWA #:	FWA00012755
UNC IRB Protocol #:	09-1362
HSRRO Project #:	A10-003CS

cc: Robert Truckner

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF THE
SCIENCE ADVISOR

MEMORANDUM

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: Deepika Polineni
Director, NHEERL Human Research Protocol Office

SUBJECT: Exemption Determination for Research Involving Human Subjects

DATE: February 2, 2012

I have reviewed the project cited below according to the requirements of EPA Order 1000.17 Change A1 **(Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research)** and have determined that during the course of the project, EPA will be engaged in research involving human subjects that is exempt from EPA Regulation 40 CFR 26 **(Protection of Human Subjects)** by virtue of belonging to category (4) under 40 CFR 26.101(b). An EPA scientist is in possession of coded identifiable specimens and will recode them in such a way that they will no longer be linked to any identifying information through a key, thus qualifying for the category (4) exemption. Once deidentified in this manner, the specimens will be shared with the project's principal investigator at another institution who will then be working only with deidentified specimens under circumstances in which reidentification is no longer possible. The principal investigator's institution, therefore, will not be engaged in human subjects research at all under the regulations. Accordingly, approval is granted for the project to proceed as proposed.

Project Title: *Albumin Adducts as Measures of Total Human Exposure*

Principal Investigator: Stephen Rappaport

EPA Co-Investigator: Jane Gallagher

HSRRO Project #: A12-003CS

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF THE
SCIENCE ADVISOR

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Approval of Research Involving Human Subjects

DATE: February 14, 2012

I have reviewed the study cited below according to the requirements of EPA Order 1000.17 Change A1 **(Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research)** and have determined that it qualifies as intentional exposure research involving human subjects that complies with EPA Regulation 40 CFR 26 **(Protection of Human Subjects)**. The finding of compliance includes the determination that the research is non-exempt under 40 CFR 26.101(b), that it has been approved by the IRB of record, and that the institutions engaged in the research have valid Federalwide Assurances on file with the HHS Office for Human Research Protections. Accordingly, approval is granted for recruitment and enrollment of human research subjects at the UNC-EPA study site. (This study was previously approved at all original study sites under HSRRO Study # E11-030CS. The current approval is for a revised protocol at the UNC site in the EPA Human Research Facility in Chapel Hill, NC with the addition of an EPA co-investigator.)

Study Title:	*Multicenter Ozone Study of Elderly Subjects (MOSES)*
Engaged Institutions:	University of North Carolina at Chapel Hill National Health & Environmental Effects Research Laboratory, U.S. Environmental Protection Agency
FWA #s:	FWA00004801 (UNC-CH) FWA00012755 (NHEERL, USEPA)
Principal Investigator:	Philip Bromberg
HSRRO SAA#s:	E07-007F (CEMALB) E10-027F (Health Effects Institute)
HSRRO Study #:	B12-013CS

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF THE
SCIENCE ADVISOR

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Approval of Research Involving Human Subjects

DATE: February 21, 2012

I have reviewed the study cited below according to the requirements of EPA Order 1000.17 Change A1 **(Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research)** and have determined that it qualifies as observational research involving human subjects that complies with EPA Regulation 40 CFR 26 **(Protection of Human Subjects).** The finding of compliance includes the determination that the research is non-exempt under 40 CFR 26.101(b), that it has been approved by the IRB of record, and that the institution engaged in the research has a valid Federalwide Assurance on file with the HHS Office for Human Research Protections. Accordingly, approval is granted for recruitment and enrollment of human research subjects into the study.

Study Title:	*Observational Study of the Effects of Ambient Air Pollution Exposure in Adults with Established Coronary Heart Disease*
Engaged Institution:	U.S. Environmental Protection Agency, National Health & Environmental Effects Research Laboratory
FWA #:	FWA00012755
UNC IRB Study #:	11-1867
Principal Investigator:	Martha Sue Carraway
HSRRO Study #:	B12-015CS

CC: Deepika Polineni, Director, NHEERL Human Research Protocol Office

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 15 2013

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Approval of Research Involving Human Subjects

FROM: Robert Kavlock, Ph.D.
Interim EPA Human Subjects Research Review Official (HSRRO)

TO: Ronald N. Hines, Ph.D.
Associate Director for Health
National Health and Environmental Effects Research Laboratory

I have reviewed the application cited below according to the requirements of Environmental Protection Agency Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as observational research involving human subjects and that it complies with EPA Regulation 40 CFR 26 (**Protection of Human Subjects**). The finding of compliance includes the determination that the research is non-exempt under 40 CFR 26.101(b), that it has been reviewed and approved by the IRB with jurisdiction over the research, and that the institutions engaged in the research have valid Federalwide Assurance numbers on file with the HHS Office for Human Research Protections. Accordingly, approval is granted for the study to proceed.

Application Title:	Observational Assessment of Baseline Asthma Control as a Susceptibility Factor for Air Pollution Health Effects in African-American Children with Moderate-Severe Asthma (Teen AIRE Study)
Engaged Institution:	ORD NHEERL
Federalwide Assurance#:	FWA 00004801 (UNC at Chapel Hill Biomedical IRB)
EPA Project Officer:	Michael Schmitt, EPHD, NHEERL
HSRRO Project#:	B13-027C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF THE
SCIENCE ADVISOR

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Approval of Research Involving Human Subjects

DATE: June 10, 2010

I have reviewed the project cited below according to the requirements of EPA Order 1000.17 Change A1 **(Policy and Procedures on Protection of Human Research Subjects)** and have determined that it qualifies as intentional exposure research involving human subjects that complies with EPA Regulation 40 CFR 26 **(Protection of Human Subjects)**. Accordingly, approval is granted for recruitment and enrollment of human research subjects into the study.

Project Title:	*Cardiopulmonary Responses to Exposure to Ozone and Diesel Exhaust with Moderate Exercise in Healthy Adults (DEPOZ)*
Institution:	U.S. Environmental Protection Agency National Health and Environmental Effects Research Laboratory
FWA #:	FWA00012755
UNC IRB Protocol #:	09-1344
Principal Investigator:	Tina Stevens
HSRRO Project #:	C10-018CS

cc: Robert Truckner

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

DATE: March 30, 2010

SUBJECT: Result of HSRRO Review of Research Involving Human Subjects

- **Project Title:** *Cardiopulmonary Responses to Exposure to Ozone and Diesel Exhaust with Moderate Exercise in Healthy Adults*
- **Principal Investigator:** Tina Stevens
- **Engaged Institution:** U.S. Environmental Protection Agency (National Health and Environmental Effects Research Laboratory)
- **FWA #:** FWA00012755
- **UNC IRB Protocol #:** 09-1344
- **HSRRO Project #:** C10-018CS

I have reviewed the project cited above according to the requirements of EPA Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as intentional exposure research involving human subjects that requires revision in order to qualify for HSRRO approval of the research. There are two significant issues for which revision is mandatory. There is also a suggestion for improvement, which is not in itself disqualifying.

Issue #1: The protocol refers to many, if not most, of the measurements, collections, and specimen analyses as activities that "may" be undertaken. Thus, these are left to investigator discretion, rather than being required by the protocol and reportable as protocol deviations if not undertaken. If *all* the "mays" that currently exist in this protocol are, in fact, undertaken, the research will likely achieve its stated aims. If *none* of them are undertaken, however, it is unlikely that the research will produce useful data. If it is something in between these extremes, it is impossible to know what kind of

outcome will occur without knowing which measurements, collections, and specimen analyses are retained and which are not. It is acknowledged that investigator flexibility confers certain critical advantages at some stages of some research, particularly during the research development phase. Once human subjects are involved in research of the sort contemplated here, however, the protocol needs to include a more definitive commitment to what data will be acquired than is currently present in order for reviewers to evaluate adequately the likelihood that the research aims will be met. Moreover, such review is a critical part of the ethical analysis, since the involvement of human subjects is justified only when there is a reasonable likelihood that the research will produce valid and useful results. If circumstances encountered during the course of conducting the research require deviation from a protocol previously determined to be adequate to generate valid and useful results, then evaluating them *as protocol deviations* is critical to the decision of those monitoring the research as to whether or not the research should be allowed to continue with the involvement of human subjects. The modification required to address this issue is to replace "may" with "will" for a sufficient number of measurements, collections, and specimen analyses that reviewers can be assured that research aims will be met if the protocol is carried out as written.

Issue #2: Both the protocol and the consent form discuss the risks from combined exposure to ozone and diesel exhaust as being additive, not synergistic, although that is, in fact, not known. Indeed, one of the aims of the research is to fill this knowledge gap, as the protocol itself acknowledges. It is one thing to examine the effects of the two exposures using the *hypothesis* that the effects are additive, but it is quite another to apply this to the risk disclosure statement in advance of finding out the definitive answer. In fact, the risks that might be present here are not yet known, and that needs to be disclosed to the potential participants. Reassuring statements about the expectation that risks will be additive are not adequately evidence-based and may mislead persons considering participation in the research. Moreover, it is ethically preferable to discuss this absence of knowledge about risk in the specific context in which it occurs, where possible, rather than rely exclusively on the more general boilerplate language about "previously unrecognized risks" contained in most consent forms, including the one proposed for this study. The current consent form reads: "While this exposure scenario has not been conducted at our facilities before, we anticipate this exposure will include the same risks as diesel exhaust and ozone exposures alone. Therefore, we do not expect the combination of diesel exhaust and ozone to increase the effects of each pollutant individually." The disclosure that more accurately reflects the facts would read: "Because this exposure scenario has not been conducted at our facilities or elsewhere before, we do not yet know whether or not this exposure will include the same risks as diesel exhaust and ozone exposures alone. It is possible that the combination of diesel exhaust and ozone exposures will increase the effects of each pollutant individually, and it is also possible that it will not. We are doing this study in order to find out the answer."

Suggestion: The recruitment materials refer to the minimum age (18) but do not discuss the exclusion of pregnant or nursing women. The exclusions are fully disclosed and discussed in the protocol and consent form, so there is no compliance issue here and no reasonable chance that an excluded subject might be entered into the study. However, it would still not be unreasonable to disclose this exclusion up-front during the recruitment stage and so make this even clearer for anyone looking at this research from the outside. Again, however, this is only a suggestion and not a mandatory change necessary for approval of the research by the HSRRO as compliant with 40 CFR 26.

cc: Robert Truckner

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF THE
SCIENCE ADVISOR

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: John Vandenberg
Director, RTP Division
National Center for Environmental Assessment

SUBJECT: Approval of Research Involving Human Subjects

DATE: March 27, 2012

I have reviewed the study cited below according to the requirements of EPA Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as observational research involving human subjects that complies with EPA Regulation 40 CFR 26 (**Protection of Human Subjects**). Accordingly, approval is granted for the participation of EPA investigators in the research.

Study Title:	*A Tenacious Toxin: Mercury Contamination and Residential Exposure in Huancavelica, Peru and Potosi, Bolivia*
EPA Component:	National Center for Environmental Assessment
EPA FWA #:	FWA00012755
Lead EPA Investigator:	John Vandenberg
UNC IRB Study #:	11-0787
HSRRO Study #:	C12-022CS

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF THE
SCIENCE ADVISOR

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Approval of Research Involving Human Subjects

DATE: April 23, 2010

I have reviewed the project cited below according to the requirements of EPA Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as observational research involving human subjects that complies with EPA Regulation 40 CFR 26 (**Protection of Human Subjects**). Accordingly, approval is granted for recruitment and enrollment of human research subjects into the study.

Project Title:	*Series of Case-Patients with Nontuberculous Mycobacteria Isolation, Central North Carolina, 2006-2010*
Institution:	U.S. Environmental Protection Agency National Health and Environmental Effects Research Laboratory
FWA #:	FWA00012755
UNC IRB Protocol #:	09-1843
Principal Investigator:	Elizabeth Hilborn
HSRRO Project #:	D10-020CS

cc: Robert Truckner

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF THE
SCIENCE ADVISOR

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Approval of Research Involving Human Subjects

DATE: May 24, 2010

I have reviewed the project cited below according to the requirements of EPA Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as intentional exposure research involving human subjects that complies with EPA Regulation 40 CFR 26 (**Protection of Human Subjects**). Accordingly, approval is granted for recruitment and enrollment of human research subjects into the study.

Project Title:	*Epigenetic Effects of Diesel Exhaust and Ozone Exposure*
Institution:	U.S. Environmental Protection Agency National Health and Environmental Effects Research Laboratory
FWA #:	FWA00012755
UNC IRB Protocol #:	09-1625
Principal Investigators:	Melanie Jardim David Diaz-Sanchez
HSRRO Project #:	E10-025CS

cc: Robert Truckner

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Approval of Research Involving Human Subjects

DATE: July 13, 2011

I have reviewed the study cited below according to the requirements of EPA Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as intentional exposure research involving human subjects that complies with EPA Regulation 40 CFR 26 (**Protection of Human Subjects**). The finding of compliance includes the determination that the research is non-exempt under 40 CFR 26.101(b), that it has been approved by the IRB of record, and that the institution engaged in the research has a valid Federalwide Assurance on file with the HHS Office for Human Research Protections. Accordingly, approval is granted for recruitment and enrollment of human research subjects into the study.

Study Title:	*Interaction Effects of Temperature and Ozone*
Engaged Institution:	U.S. Environmental Protection Agency National Health and Environmental Effects Research Laboratory
FWA #:	FWA00012755
UNC IRB Protocol #:	11-0772
Principal Investigator:	David Diaz-Sanchez
HSRRO Project #:	G11-056CS

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

FROM: Warren Lux
EPA Human Subjects Research Review Official

OFFICE OF THE
SCIENCE ADVISOR

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Approval of Research Involving Human Subjects

DATE: August 20, 2010

I have reviewed the project cited below according to the requirements of EPA Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as intentional exposure research involving human subjects that complies with EPA Regulation 40 CFR 26 (**Protection of Human Subjects**). The finding of compliance includes the determination that the research is non-exempt under 40 CFR 26.101(b), that it has been approved by the IRB of record, and that the institution engaged in the research has a valid Federalwide Assurance on file with the DHHS Office for Human Research Protections. Accordingly, approval is granted for recruitment and enrollment of human research subjects into the study.

Project Title:	*Cardiopulmonary Effects of Exposure of Healthy Older Individuals to Exhaust from a High Efficiency Diesel Generator (COPILOT)*
Engaged Institution:	U.S. Environmental Protection Agency National Health and Environmental Effects Research Laboratory
FWA #:	FWA00012755
UNC IRB Protocol #:	10-0187
Principal Investigator:	James Samet
HSRRO Project #:	H10-045CS

Cc: Tim Watkins
Robert Truckner

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

SUBJECT: Approval of Research Involving Human Subjects

DATE: September 19, 2011

I have reviewed the study cited below according to the requirements of EPA Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as observational research involving human subjects that complies with EPA Regulation 40 CFR 26 (**Protection of Human Subjects**). The finding of compliance includes the determination that the research is non-exempt under 40 CFR 26.101(b), that it has been approved by the IRB of record, and that the institutions engaged in the research have valid Federalwide Assurances on file with the HHS Office for Human Research Protections. Accordingly, approval is granted for recruitment and enrollment of human research subjects into the study.

Study Title:	*Particulate Matter, Environmental Quality, and Birth Outcomes*
Engaged Institutions:	University of North Carolina at Chapel Hill U.S. Environmental Protection Agency, NHEERL
FWA #s:	FWA00004801 (UNC-CH) FWA00012755 (U.S. EPA)
UNC-CH IRB Protocol #:	11-1089
Principal Investigator:	Kristen Rappazzo
HSRRO Project #:	I11-067CS

CC: Howard Kehrl
Danelle Lobdell